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| APPLICATION NO.             | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.  | CONFIRMATION NO. |
|-----------------------------|-------------|----------------------|----------------------|------------------|
| 10/701,236                  | 11/04/2003  | Brenda F. Baker      | ISIS-5207            | 5280             |
| 32650                       | 7590        | 07/10/2008           | EXAMINER             |                  |
| WOODCOCK WASHBURN LLP       |             |                      | VIVLEMORE, TRACY ANN |                  |
| CIRA CENTRE, 12TH FLOOR     |             |                      |                      |                  |
| 2929 ARCH STREET            |             |                      | ART UNIT             | PAPER NUMBER     |
| PHILADELPHIA, PA 19104-2891 |             |                      | 1635                 |                  |
|                             |             |                      | MAIL DATE            | DELIVERY MODE    |
|                             |             |                      | 07/10/2008           | PAPER            |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/701,236             | BAKER ET AL.        |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Tracy Vivlemore        | 1635                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 16 June 2008.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1 and 71-79 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1 and 71-79 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

|  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                         | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|  | 6) <input type="checkbox"/> Other: _____ .                        |

## **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The finality of the last office action is withdrawn and prosecution re-opened in view of the following rejections.

Any rejection or objection not reiterated in this Action is withdrawn.

### ***Double Patenting***

Claims 1 and 71-79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 19-22, 54, 57 and 63 of copending Application No. 10/700,697. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '697 application are directed to modified duplex RNAs comprising 2'-substitutions, which are a species that anticipates the claims of the instant application, which are directed generically to duplex RNAs comprising sugar surrogates. The term sugar surrogate is not explicitly defined in the instant specification, but is described only by exemplification. Contemplated sugar surrogates include arabino nucleotides, pyrrolidine nucleotides and 4'-thioribose nucleotides. In view of the lack of an explicit definition for the term sugar surrogate, this term is interpreted as any entity other than the naturally occurring ribose nucleoside that is capable of use in an oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 71-79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,7-9,16,18-22,26-31,73 and 76-85 of copending Application No. 10/701,264. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '264 application are directed to modified duplex RNAs comprising 2'-OMe substitutions, which are a species that anticipates the claims of the instant application, which are directed generically to duplex RNAs comprising sugar surrogates. The term sugar surrogate is not explicitly defined in the instant specification, but is described only by exemplification. Contemplated sugar surrogates include arabino nucleotides, pyrrolidine nucleotides and 4'-thioribose nucleotides. In view of the lack of an explicit definition for the term sugar surrogate, this term is interpreted as any entity other than the naturally occurring ribose nucleoside that is capable of use in an oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 71-79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 11, 75, 78 and 93-97 of copending Application No. 10/701,316. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '316 application are directed to modified duplex RNAs comprising 2'-substitutions, which are a species that anticipates the claims of the instant application, which are directed

generically to duplex RNAs comprising sugar surrogates. The term sugar surrogate is not explicitly defined in the instant specification, but is described only by exemplification. Contemplated sugar surrogates include arabino nucleotides, pyrrolidine nucleotides and 4'-thioribose nucleotides. In view of the lack of an explicit definition for the term sugar surrogate, this term is interpreted as any entity other than the naturally occurring ribose nucleoside that is capable of use in an oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

#### ***Response to Arguments: Double Patenting***

Applicants' request that the provisional double patenting rejections be held in abeyance until claims are found allowable is acknowledged, but until the rejections have been overcome, it is proper to maintain the rejections.

#### ***Claim Rejections - 35 USC § 103***

Claims 1 and 71-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. as in view of Stec et al. and Summerton et al. (all of record).

The claims are directed to compositions comprising chemically synthesized oligomers that comprise about 12 to about 30 nucleotides, are not covalently linked and are at least partially complementary to each other; at least one strand is partially complementary to a target mRNA. Each strand comprises at least one sugar surrogate and at least one strand has a plurality of 2'-hydroxy-pentofuranosyl sugar moieties. In

specific embodiments the ribonucleotides are in the second oligomer, the oligomers are chimeric oligonucleotides that may be gapmers or hemimers, one or both of the oligomeric compounds of the composition have at least one phosphorothioate linkage, the sugar surrogate is of a particular type, the oligomeric compound comprises at least two modified nucleosides. In other embodiments the mRNA is a mammalian or human mRNA.

Yu et al. teach in figure 1C a duplex comprising one strand of RNA corresponding to a 24-nucleotide portion of 28S ribosomal RNA with one 2'-OMe substitution. The other strand of the duplex is 18 nucleotides in length and comprises a chimeric gapmer oligonucleotide of 2'-OMe and 2'-deoxy nucleotides. This duplex is used in an RNase H cleavage assay, which involves formulation of the duplex as a composition with a pharmaceutically acceptable carrier. Yu et al. do not teach a duplex targeted to mRNA or teach a duplex containing phosphorothioate linkages and do not teach the use of other sugar surrogates.

It was well known in the art at the time the invention was made to incorporate modified nucleotides, including phosphorothioate linkages and modified sugars such as morpholino sugars, into an oligonucleotide for the purpose of increasing stability and exonuclease resistance. See for example, Stec et al. who teach the use of phosphorothioate linkages for these desirable properties and Summerton et al., who teach morpholino sugar groups that can be incorporated into oligonucleotides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a duplex taught by Yu et al. as useful in RNase H

cleavage assays that is targeted to an mRNA such as a mammalian mRNA in order to determine if any sites within the mRNA are methylated. It would further have been obvious to modify these duplexes with modified nucleotides such as phosphorothioate linkages or morpholino sugars in order to determine if these modifications will provide active substrates for RNase H. One of ordinary skill in the art would have had a motivation and reasonable expectation of success in doing so based on the recognition that duplexes can be designed to target any known sequence and the recognition by those in the art that use of modified nucleotides such as phosphorothioate linkages and morpholino sugars provide the advantages of increased stability and exonuclease resistance.

Thus, the invention of claims 1 and 71-79 would have been obvious, as a whole, at the time the invention was made.

### ***Response to Arguments***

Applicants traverse the 103 rejection by arguing that Yu et al. discuss duplexes in which one strand is complementary to rRNA and not to mRNA as claimed and assert that the cited references do not suggest applying the teaching of Yu to mRNA.

This is not persuasive because one of ordinary skill in the art would recognize the duplexes taught by Yu et al. could be readily modified to target any sequence, including mRNA and that this is a matter of design choice.

Applicants further argue that one skilled in the art would have no reason to modify the native rRNA to enhance or inhibit nuclease activity, asserting that such modification would frustrate the purpose of the assay described in Yu.

This is not persuasive because the assay described in Yu is an RNase H assay, which is an endonuclease. The modifications taught by Stec et al. and Summerton et al. provide exonuclease resistance and would have no affect on the assay described by Yu et al.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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